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Epigenetic aging of mammalian gametes

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Abstract

The process of aging refers to physiological changes that occur to an organism as time progresses and involves changes to DNA, proteins, metabolism, cells, and organs. Like the rest of the cells in the body, gametes age, and it is well established that there is a decline in reproductive capabilities in females and males with aging. One of the major pathways known to be involved in aging is epigenetic changes. The epigenome is the multitude of chemical modifications performed on DNA and chromatin that affect the ability of chromatin to be transcribed. In this review, we explore the effects of aging on female and male gametes with a focus on the epigenetic changes that occur in gametes throughout aging. Quality decline in oocytes occurs at a relatively early age. Epigenetic changes constitute an important part of oocyte aging. DNA methylation is reduced with age, along with reduced expression of DNA methyltransferases (DNMTs). Histone deacetylases (HDAC) expression is also reduced, and a loss of heterochromatin marks occurs with age. As a consequence of heterochromatin loss, retrotransposon expression is elevated, and aged oocytes suffer from DNA damage. In sperm, aging affects sperm number, motility and fecundity, and epigenetic changes may constitute a part of this process. 5 methyl-cytosine (5mC) methylation is elevated in sperm from aged men, but methylation on Long interspersed nuclear elements (LINE) elements is reduced. Di and trimethylation of histone 3 lysine 9 (H3K9me2/3) is reduced in sperm from aged men and trimethylation of histone 3 lysine 27 (H3K27me3) is elevated. The protamine makeup of sperm from aged men is also changed, with reduced protamine expression and a misbalanced ratio between protamine proteins protamine P1 and protamine P2. The study of epigenetic reproductive aging is recently gaining interest. The current status of the field suggests that many aspects of gamete epigenetic aging are still open for investigation. The clinical applications of these investigations have far-reaching consequences for fertility and sociological human behavior.

KEYWORDS

aging, DNA methylation, epigenetic modifications, gametes, oocytes, sperm

1 | INTRODUCTION

Haploid gametes and their diploid progenitors are unique cells in the body, being the only cells that hold the capacity to transmit their genetic material to the next generations. Therefore, understanding the development of these cells, along with the mechanisms involved in maintaining DNA integrity is extremely important, as improper function may lead to various pathologies such as infertility and genetic diseases. Moreover, mechanisms that maintain the capability of the gametes to remain totipotent and uncommitted to any differentiation fate before fertilization are of great importance for proper embryogenesis.

The process of aging refers to physiological changes that occur as the organism ages, and involves changes to the DNA, proteins, metabolism, cells, and organs. Similar to all the cells in the body, gametes age as well, and it is established that there is a decline in reproductive capabilities in females and males (Gunes et al., 2016). However, female gametogenesis is one of the fastest-aging cellular systems in mammals, and reproductive aging has been considered as the earliest sign of aging in humans (Llarena & Hine, 2021; Yureneva et al., 2021).

Female reproductive aging has a large impact on population makeup, population growth trends, and how reproduction is perceived worldwide (Leridon & Slama, 2008; Neels et al., 2013; Okine et al., 2023; Safdari-Dehcheshmeh et al., 2023; Schmidt et al., 2012). In recent decades, many couples choose to postpone having children due to various socioeconomic reasons, and hence it is critical to thoroughly explore the effects of aging on gametes (Gunes et al., 2016; Schmidt et al., 2012). Indeed, female age at first birth has increased by 2–4 years over the past 20–30 years, surpassing the age of 30 in many countries (Safdari-Dehcheshmeh et al., 2023). Regarding male aging patterns, reports from the US indicate that in 2013 there was a 14% increase in paternal age of men aged 40–44 and 16% of men aged 50–54 compared to the previous decade (Martin et al., 2015; Yatsenko & Turek, 2018). Similar trends are also seen in the United Kingdom and other countries (Bray, 2006). This delay in childbearing practically shortens the time window for reproduction and brings many more couples to be reproductively challenged and seek medical help (Safdari-Dehcheshmeh et al., 2023).

Aging is known to be tightly linked to many biological processes and pathways, some of which have been coined as the "hallmarks of aging" (Lopez-Otin et al., 2013). One of the major pathways which is known to be involved in aging is epigenetic changes (Lopez-Otin et al., 2023; Owczarz et al., 2020; Sikder et al., 2022; Singh et al., 2013; Soto-Palma et al., 2022; Tennen et al., 2011; Yang et al., 2023).

The epigenome is the multitude of chemical modifications performed on chromatin that affect the ability of chromatin to be transcribed. In contrast to genetic changes in the DNA itself, epigenetic changes can be more easily reversed, and are affected by signaling pathways and changes in the cellular and external environment. Similar to genetic changes, epigenetic changes can be inherited both through cell divisions and even between generations (Budhavarapu et al., 2013; Nicolella & de Assis, 2022; Oomen & Dekker, 2017; Tuscher & Day, 2019). Classically, epigenetic changes can be classified into three main categories: DNA methylation, histone modifications, and noncoding RNAs (Allis & Jenuwein, 2016).

DNA methylation involves the addition of a methyl group to cytosine residues located in cytosine phosphate guanine (CpG) dinucleotides. It is well established that methylation patterns at gene promoters and regulatory regions have the capacity to impact gene transcription (Portela & Esteller, 2010). High level of CpG methylation at gene promoters, referred to as hypermethylation, is known to facilitate gene repression (Paroush et al., 1990), whereas low levels of methylation, referred to as hypomethylation, mediates gene activation (Pollard & Jenkins, 2020). Changes in DNA methylation in aging have been actively investigated in the last decades (Alimohammadi et al., 2022; Klutstein et al., 2016, 2017; Vaidya et al., 2023; Zhou et al., 2018), and molecular aging clocks based on DNA methylation have been developed (Horvath & Raj, 2018).

Histone modifications are chemical changes to amino acids on histones, usually in the N-terminal tail protruding out of the globular nucleosome structure. Modification of histones can serve to activate transcription-known as euchromatic modifications (e.g., trimethylation of histone 3 lysine 4-H3K4me3), or repress transcription-known as heterochromatic modifications (e.g., di and trimethylation of histone 3 lysine 9-H3K9me2/3, trimethylation of histone 3 lysine 27-H3K27me3) (Allis & Jenuwein, 2016). Changes to histone modifications enzymes and the levels of histone modifications have been shown to be involved in aging processes (Ghiraldini et al., 2013; Kanfi et al., 2012; Lee et al., 2021; Saul & Kosinsky, 2021; Wood et al., 2010; Yi & Kim, 2020). Noteworthy are changes in the *Sirtuin* family members of HDACs, that were among the first genes to be shown involved in cellular aging (Gámez-García & Vazquez, 2021; Ghiraldini et al., 2013; Kaeberlein et al., 1999; Watroba & Szukiewicz, 2021). Changes in *Sirt6* and *Sirt1* have been extensively shown to affect aging-related phenotypes (Mostoslavsky et al., 2006; Owczarz et al., 2020; Simon et al., 2022; Singh et al., 2013; Tennen et al., 2011; Zia et al., 2021).

Noncoding RNAs associated with chromatin are an emerging theme in epigenetic research, and so far-the least investigated arm of epigenetic modifications (Allis & Jenuwein, 2016). Noncoding RNAs are associated with both activation and repression of transcription and their landscape is complex. Noncoding RNAs have also been associated with aging and aging-related phenotypes (Hamdan et al., 2021; Kato et al., 2011; Kulaberoglu et al., 2021; Saka et al., 2013; Shigematsu et al., 2019; Yang et al., 2023). Less is known regarding noncoding RNAs in gametes and how they change with age, and therefore this topic will not be discussed further below. We thus focus on DNA methylation and histone modifications.

In this review, we explore the effects of aging on the female and male gametes with a focus on the epigenetic changes that occur in gametes throughout aging (see summary in Figure 1). We describe the effects these changes have on the gametes functions and their ability to produce a viable embryo.

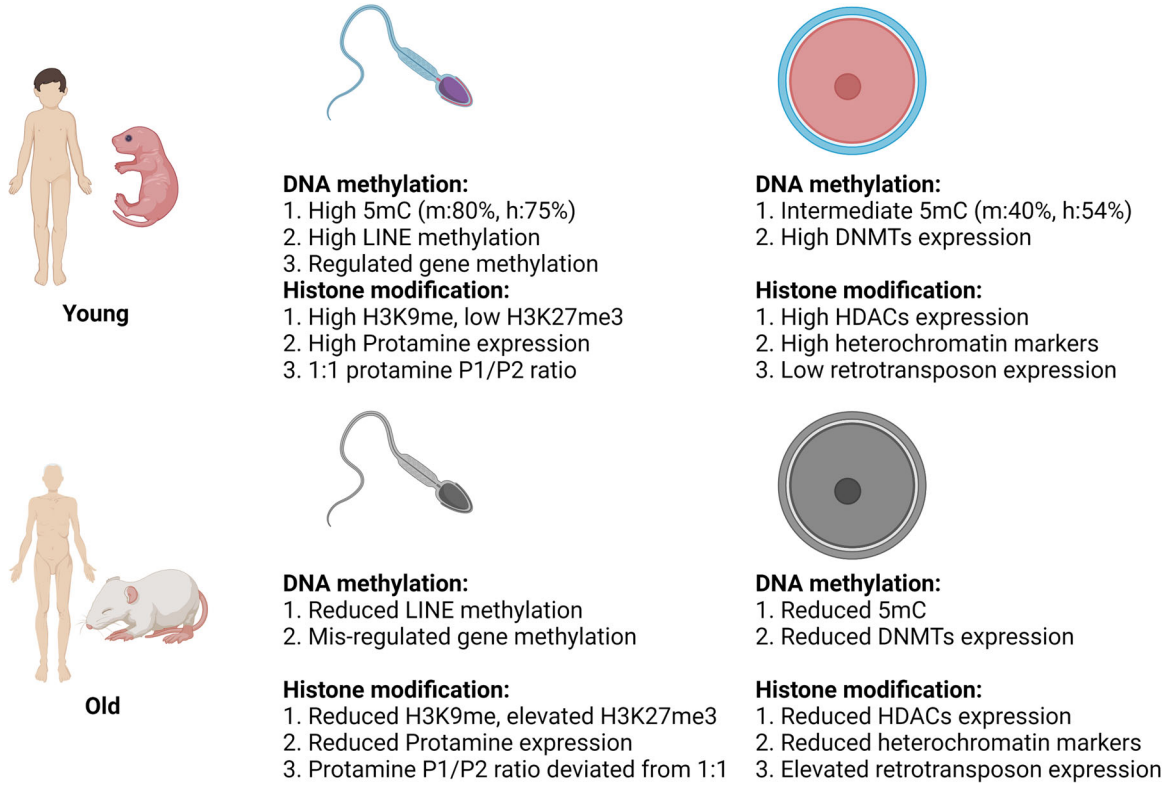

FIGURE 1 Summary of epigenetic changes in gamete aging: Depicted are the main known epigenetic changes that occur in aged gametes (lower part) compared to young gametes (upper part). We discuss both male gametes (left panels) and female gametes (right panels). Figure generated using BioRender. DNMTs, DNA methyltransferases; h, human; HDACs, histone acetyltransferases; LINE, long interspersed nuclear elements; m, mouse; 5mC, 5 methylcytosine; H3K9me2, methylation of histone 3 lysine 9; H3K27me3, methylation of histone 3 lysine 27.

2 | OOCYTE AGING

Female reproductive aging mainly occurs due to diminished oocyte quality with age that lowers reproductive success in older females (Duncan & Gerton, 2018; Igarashi et al., 2015). The dependence of female reproductive aging on oocyte quality is well demonstrated by the elevated reproductive performance of older IVF patients who have received an egg donation from a young donor- compared to age-matched patients using their own eggs (Wang, Farquhar, et al., 2012).

2.1 | Who is considered an aged female?

Focusing on the onset age for oocyte quality deterioration—it is difficult to assess whether this is a continuous process or whether it starts at a specific age. Moreover, the rate of deterioration is different between different species, and among different genetic backgrounds (in mice, for example) (Dutta & Sengupta, 2016). However, the comparison of reproductive aging between species is under active debate, and some researchers have tried to compare human and mouse reproductive aging and calculated time to reproductive senescence by using 8.82 days in mice for 1 year in humans (Dutta & Sengupta, 2016). However, in the human population, oocyte quality and its deterioration with age is an extremely variable trait, and heavily depends on genetics and environmental determinants in the human population (Gianaroli et al., 2010; te Velde, 2002). The guidelines for oocyte donation by the American Society for Reproductive Medicine state that: "Oocyte donors should preferably be between the ages of 21 and 34. If a prospective donor is over 34 years of age, the age of the donor should be revealed to the recipient as part of the informed consent discussion concerning cytogenetic risks and the effect of donor age on pregnancy rates" (American Society for Reproductive Medicine, 2004). This should serve as a general guideline for which maternal age is already considered problematic for assisted reproductive technologies (ART).

The aspect of oocyte quality that has been studied the most over the last few decades is the occurrence of oocyte aneuploidy with age, which seems to be a continuous process both in human oocytes (Gruhn et al., 2019) and in mouse oocytes (Merriman et al., 2012) with a steep increase in the late 30 s in human and after 12 months of age in C57BL/6 mice (Gruhn et al., 2019; Merriman et al., 2012). More research is needed on different aspects of oocyte quality, to determine the specific age of onset of aging phenotypes for each aspect of female reproductive aging.

2.1.1 | Effects of maternal age on reproduction

Hormones and ovarian functions

The number of available oocytes for female reproduction is limited throughout life, as females are born with a finite number of oocytes and do not produce more throughout their lifetime. Moreover, ovarian reserve diminishes further due to tight quality control mechanisms in the ovary, that lower the number of available oocytes with age. As females age, the decline in oocyte quantity leads to a decrease in fertility potential (Broekmans et al., 2009). Less follicles are produced with age at each cycle, and those follicles are smaller. This leads to a reduction in ovary size with age (Pavlik et al., 2000). Recent studies have shown that ovarian stiffness (fibrosis) increases with age, depending on changes in the collagen and hyaluronan matrices in the ovary (Amargant et al., 2020). Immune cell infiltration into the aging ovary may also contribute to structural ovarian changes with age (Foley et al., 2021).

Diminished ovarian reserve and the resulting decrease in secreted sex hormones from the ovary have important implications for the hormonal makeup of aging females. The most significant hormonal change is the decline in estrogen, which leads to adverse health implications such as bone loss, elevated risk of heart disease, and mood changes (Horstman et al., 2012). Additionally, progesterone also decreases with female age. This decrease also impacts female health and is related to loss of menstrual cycles, headaches, mood changes, hot flashes, and weight gain (O'Connor et al., 2009; Singh, 2005). On the other hand, rising female age leads to elevated levels of FSH and LH produced by the pituitary gland (Reame et al., 1996). It is unclear if this rise is only the result of feedback mechanisms in the brain, elevating the levels of secreted FSH/LH in response to the decrease in estrogen and progesterone, or whether it has additional roles. It is possible that the rise in FSH/LH causes diminished fertility on its own (McTavish et al., 2007).

Oocyte aneuploidy

In human ART patients live birth rate in in vitro fertilization (IVF) is reduced from 19.2% at the age of 38 to 5.1% at the age of 43 (Armstrong & Akande, 2013). Advanced maternal age correlates with oocyte chromosomal aberrations and aneuploidies that lead to genetic disorders like Down syndrome (Allen et al., 2009). Recent evidence shows that some of age-related oocyte aneuploidy stems from loss of cohesin units from chromatin during oocyte arrest. Cohesin is a protein ring that binds sister chromatids and keeps them joined throughout interphase and the first part of meiotic and mitotic prophase. Cohesin units cannot be reloaded and therefore any lost cohesin unit contributes to an elevated risk of nondisjunction of sister chromatids in meiosis I (MI) and aneuploidy (Burkhardt et al., 2016; Hodges et al., 2005; Jessberger, 2012; Revenkova et al., 2010). Additional causes for oocyte aneuploidy such as the involvement of aberrant positions and levels of homologous recombination events (Capalbo et al., 2017; Ottolini et al., 2015), as well as depletion of Shugoshin (a protein that binds kinetochores and regulates cohesion of sister chromatids and kinetochore microtubule attachment) in mouse oocytes (Lister et al., 2010) and meiotic spindle abnormalities in mouse and human oocytes (Blengini et al., 2021; Holubcova et al., 2015) have been suggested. The rise in aneuploidy and concurrent deterioration of the levels of various chromatin factors such as Cohesin and Shugoshin could be also linked to epigenetic changes. In principle, it may be possible to elucidate a model that places cohesion dysfunction, kinetochore instability, and spindle deformations downstream of loss of key epigenetic features such as pericentric heterochromatin (Klutstein, 2021). However, experiments designed to specifically link these mechanisms have not been described yet. Moreover, it is still not entirely clear how the epigenome of oocytes changes with age and what are the mechanisms that lead to such changes.

Offspring health

As a direct result of oocyte aneuploidy, embryogenesis of the offspring becomes less successful with age, and many embryos arrest and fail to develop. Therefore, the main offspring health outcome related to maternal age is the high occurrence of aneuploidy-related syndromes, mainly Down syndrome (but also trisomy 18- Edwards syndrome and trisomy 13- Patau syndrome) (Cuckle & Morris, 2021). Evidence also exists as to the correlation between advanced maternal age and other chromosome aneuploidies such sex chromosomes aneuploidies (e.g., 45, X and 47, XXY) (Li et al., 2021; Yaegashi et al., 1998). Some studies have found an association between advanced maternal age and a higher risk of ADHD and learning disabilities (Gao et al., 2023), as well as a higher risk of diabetes (Gale, 2010). However, other studies have doubted these findings and have established that advanced maternal age and offspring adult health associations reflect mostly selection and factors related to lifespan overlap (Myrskylä & Fenelon, 2012).

2.1.2 | Epigenetic changes in oocytes along their lifespan

The epigenetic changes that mammalian (mouse and human) oocytes undergo during their initial development are highly dynamic and include several stages of epigenetic programming that occur before the oocytes are fully developed (Anvar et al., 2021; Eleftheriou et al., 2022; Hanna et al., 2022; Saitou, 2021; Seah & Messerschmidt, 2018; Stewart et al., 2015; Wasserzug-Pash & Klutstein, 2019; Wu et al., 2014). These programming steps include an erasure of DNA methylation to a "ground state" in primordial germ cells. Further development of oocytes in the embryonic ovary is done under this low methylation state (Gkountela et al., 2015; Guibert et al., 2012; Guo et al., 2015; Seisenberger et al., 2012; Tang et al., 2015; Yamaguchi et al., 2013). The epigenome becomes much more stable once the oocyte has reached the cell cycle arrest stage (dictyate stage) during embryonic development (Fan et al., 2021; He et al., 2021; Hu et al., 2022; Spradling et al., 2022). Oocytes are arrested then before the initiation of MI and await signals that will initiate ovulation (Wang & Pepling, 2021). Just before birth, a

selection-based event termed Fetal Oocyte Attrition reduces mouse and human oocytes numbers by ~75% (Rodrigues et al., 2009). The mechanisms leading to this event have been investigated in mouse models by several labs (Coutandin et al., 2016; Ghafari et al., 2009; Martinez-Marchal et al., 2020; Rinaldi et al., 2017; Wen et al., 2019) showing heavy involvement of DNA damage surveillance mechanisms. Notably, the Bortvin lab (Malki et al., 2014, 2019; Tharp et al., 2020), have shown an involvement of activation of retrotransposons and activation of a DNA damage checkpoint in the destroyed oocytes. It is possible that the activation of retrotransposons, upon which the selection mechanism is based, stems from epigenetic differences in the oocyte pool before birth, but this aspect has not been investigated yet.

After birth, the epigenome of resting oocytes remains largely unchanged until each oocyte develops when the follicle bearing it reacts to growth signals and becomes activated. DNA methylation acquisition also occurs at this stage in growing oocytes (Kaneda et al., 2004; Kobayashi et al., 2012; Lees-Murdock, Lau, et al., 2008; Lees-Murdock & Walsh, 2008; Okae et al., 2014). Gains in methylation during mouse and human follicular growth are widely associated with developmental genes which are already expressed at this stage, and with methylation in their gene bodies (Gahurova et al., 2017; Gu et al., 2019). Methylation changes also occur in promoter regions during this process, but the overall picture is complex as some promoters gain methylation but most remain unchanged (Chen et al., 2022; Gahurova et al., 2017; Gu et al., 2019; Masala et al., 2017; Pan et al., 2012; Yan et al., 2021).

The epigenome may also change in resting oocytes during the pubertal transition. Hormonal exposure of the oocytes and surrounding niche cells, as well as structural changes that the ovary itself undergoes during puberty may trigger nuclear and epigenetic changes in mouse and human oocytes (Karavani et al., 2021; Kusuhara et al., 2021; Wasserzug Pash et al., 2023). Previous work has shown that DNA methylation changes during puberty in pig ovaries (at 160 days of age), in promoters of genes that are related to PI3K-Akt signaling pathway, GnRH signaling pathway, and insulin secretion. All these genes are important for oocyte function (Yuan et al., 2019). Moreover, our own results show the existence of an extensive chromatin remodeling event that occurs in mouse and human oocytes (mouse- at 19 days, human- before onset of menstrual bleeding) upon exposure to FSH during the pubertal transition (Wasserzug-Pash et al., 2023). This event also manifests in changes of histone modification patterns, but the specific details are still in need of further investigation.

2.1.3 | Effects of aging on oocyte epigenetics

Oocyte DNA methylation in aging

DNA methylation has been shown to change during oocyte aging (Kordowitzki et al., 2021) (Castillo-Fernandez et al., 2020) (Yue et al., 2012). Methylation clock measurements for bovine oocytes have shown that changes in DNA methylation in oocytes correlate with age as in other tissues, but the pace of change is slower than in other tissues even though oocytes start their clocks at a somewhat "older" age than other tissues (Kordowitzki et al., 2021). Since oocytes lose their function at a relatively early age, this could mean that oocyte quality loss occurs as the DNA methylation levels drop below a specific threshold, and that this threshold occurs relatively early, but this notion still needs to be experimentally investigated. In another study, the global levels of DNA methylation have shown a marked decrease, accompanied by increased variation between individual mouse oocytes in their specific methylation patterns. Interestingly, some genes (especially a class of maternal gene-effect-genes whose products are deposited in the oocyte for use by the embryo) show both DNA methylation and RNA transcription differences between young (84 days old) and aged (350 days old) mouse oocytes (Castillo-Fernandez et al., 2020). DNA methylation at the highly condensed and heterochromatic ribosomal DNA (rDNA) rises with age in aging mouse and human oocytes, as it does in aging male germ cells. The extent of this rise in methylation can vary greatly in oocytes from the same individual, showing that different oocytes can exhibit different epigenetic age (Potabattula et al., 2022). Global DNA methylation decreases with age also in mouse oocytes as shown by bisulfite sequencing analysis (Castillo-Fernandez et al., 2020) and immunofluorescence (42–56 days compared to 245–280 days old in mouse oocytes) (Yue et al., 2012). The same study shows that DNMT methyltransferase enzymes expression levels are reduced with age (42–56 days compared to 245–280 days old) in mouse oocytes (Yue et al., 2012), a fact which may explain the reduction in the maintenance of DNA methylation at the global level. Despite these initial studies, it is still not clear what is the mechanism that drives DNA methylation changes in oocytes, and whether it depends on the prolonged cell cycle arrest these cells undergo. Future studies should also address the causative role of the decrease in DNA methylation, and whether interventions in this epigenetic machinery may slow down or even reverse the course of oocyte aging.

Oocyte chromatin landscape changes in aging

Significant changes also occur with age in the landscape of histone posttranslational modifications in oocytes. HDAC expression, needed for genome silencing machinery, decreases with age in mice (21–56 days old compared to 294–315 days old) (Hamatani et al., 2004; He et al., 2019; Zhang et al., 2014). Heterochromatic marks such as H3K9me3, H3K36me2, H3K79me2, and H4K20me2 decrease with age (60–90 days old compared to 330 days old in one study and 490 days old in another study) in mouse germinal vesicle stage (GV) oocytes—an early stage of development before meiotic resumption (Manosalva & González, 2010; Marshall et al., 2018). The Klutstein lab has recently shown that the marked decrease with age in mouse oocytes (60 days compared to 270 days old) is specific to heterochromatin (Wasserzug-Pash et al., 2022). Moreover, the decrease in heterochromatin is bigger as mouse oocytes advance to MI. The decrease in heterochromatin is accompanied by the loss of repression in most repeated regions in the genomes (encompassing ~50% of the mammalian genome), including the loss of repression of retrotransposon expression and accumulation of DNA damage in aged mouse oocytes (Wasserzug-Pash et al., 2022). Manipulation of heterochromatin levels affects retrotransposon

expression, showing that retrotransposon activity is downstream of epigenetic regulation. The same study has also shown that loss of heterochromatin during mouse oocyte aging is reversible and raising heterochromatin levels through overexpression of chromatin factors or the effect of epigenetic drugs can reduce retrotransposon expression and improves old mouse oocyte in vitro maturation (Wasserzug-Pash et al., 2022). The loss of heterochromatin with age also occurs in human arrested GV oocytes from IVF treatments (Wasserzug-Pash et al., 2022). Another similar aspect of oocytes aging was shown in an earlier study focusing on NMN (nicotinamide mononucleotide, a precursor of NADH, a cofactor for processes inside mitochondria, for sirtuins and PARP enzymes), where administration of NMN and enhancement of energy metabolism in old mice improved their oocyte quality (30 days old compared to 360 days old) (Bertoldo et al., 2020). This work showed that progeny created from such an intervention approach are born and develop normally to adulthood (Bertoldo et al., 2020). However, it is tempting to suggest that the epigenetic activity of Sirtuins following NMN treatment is responsible for this effect, supporting oocyte epigenetic aging (Wasserzug-Pash et al., 2022), although an alternative explanation related to energy and metabolism is also possible.

So far, it is unclear which genomic loci are prone to histone modification changes with age in oocytes. This question is especially important in the context of loci with functional importance such as centromeres and telomeres which are extremely sensitive to heterochromatin loss during meiosis. A reduction in heterochromatin modifications at centromeres and telomeres can lead to chromosome mis-segregation and aneuploidy (Klutstein et al., 2015).

Changes in chromatin enzymes

Changes in expression and activity were also found to occur in chromatin enzymes in aged oocytes. The expression of DNMTs Dnmt1, Dnmt3a, Dnmt3b, and Dnmt3L was found to decrease in older mouse oocytes (Yue et al., 2012). In addition, the levels of TET DNA demethylases were investigated in oocyte aging. *Tet3*- the major demethylase in the germline, was shown to be overexpressed with age in mouse oocytes (Qian et al., 2015).

Regarding histone modification enzymes- the levels of *Cdc2a*- a H4K12 acetylation factor were shown to increase with mouse oocyte aging (Manosalva & González, 2009), and the HDAC enzyme *Sirt1*, was shown to be reduced with mouse oocyte aging (Manosalva & González, 2010).

All these changes in enzyme expression and activity are consistent with a reduction in heterochromatin (either at the level of DNA methylation or histone modification) with age in oocytes, as discussed above.

2.1.4 | Perspective on oocyte aging

The notion that epigenetic changes drive important processes in oocyte aging is not novel, but recently gained more evidence. However, the understanding of how these epigenetic changes drive fluctuations in gene expression, in chromatin proteins makeup, and in the activation of DNA damage and repair pathways is still lacking. The next few years will likely see important breakthroughs in the investigation of these questions.

The study of oocyte epigenetic aging has direct and crucial links to the clinic. IVF success rates are still very low for patients over 35 years old and a clinical solution for this growing group of fertility-challenged patients is very much needed. Therefore, in addition to scientific incentives for exploring oocyte aging in-depth, there are significant clinical benefits to progress in this field. Moreover, there is much need for biotechnology companies and entrepreneurs to invest in further developing pharmaceutical solutions in this field.

2.1.5 | Age-associated changes in sperm

The effect of aging on oocytes quality and quantity was discussed above and is quite well-studied (Cimadomo et al., 2018; Duncan & Gerton, 2018; Igarashi et al., 2015). However, less focus was drawn to the effect of aging on male gametes as it was evident that aged males are well capable of having healthy biological offspring (Gunes et al., 2016; Sharma et al., 2015; Yatsenko & Turek, 2018). Starting from puberty, males have the capacity to produce sperm daily, in huge excess, and hence it was estimated that even if a decrease in the quantity and/or quality of sperm does exist, this should not have a detrimental effect on the ability of an aged male to father a child. Yet, numerous studies point out that paternal age has many effects on reproductive capabilities as well as the health of the offspring (Gunes et al., 2016; Sharma et al., 2015; Yatsenko & Turek, 2018). In this section we will briefly explore the effects of paternal aging on reproduction.

2.2 | Who is considered an aged male?

There is no uniform definition of "who is considered an aged male?". There is evidence for a decrease in sperm concentration starting from the age of 34 (Auger et al., 1995; Kidd et al., 2001), yet sperm motility and semen ejaculate volume only start to decrease at the age of 43 and 45 years, respectively (Stone et al., 2013). Hence, the precise age to define a male as an "aged male" in terms of its reproductive capabilities is less clear and sharp. The British Andrology Society and American Society for Reproductive Medicine set the age of 40 years to be the upper age limit for sperm donations (American Society for Reproductive Medicine, 2002; British Andrology Society, 1999; Sharma et al., 2015). There are conflicting results in the literature regarding the effect of paternal age on fertility. Yet, there is ample evidence to indicate that the age of the father can affect many aspects of reproduction as detailed below.

2.2.1 | Effects of paternal age on reproduction

Structure and hormonal functions of the testis

Several studies indicate that testicular size, morphology, and function are negatively impacted by paternal age (Gunes et al., 2016;

Mahmoud et al., 2003; Sharma et al., 2015; Yang et al., 2011). Normally, testis volume tends to increase from puberty till the age of 30–40, be stable between the ages of 40–60 and start to decrease gradually after the age of 60 (Yang et al., 2011). Mahmoud et al. (2003) reported a 31% decrease in testicular volume in males aged >75 years compared to males aged 18–40 years. The decrease in testicular volume is speculated to be due to a decrease in the number of Sertoli cells as well as the thickness of the basal lamina membrane wrapping the seminiferous tubules (Johnson et al., 1988; Mahmoud et al., 2003). Further testicular changes in aged males include hormonal changes in the form of increased FSH serum levels and decreased testosterone levels, possibly due to the decrease in Leydig cells, which ultimately lead to lower sexual activity and poor libido (Handelsman, 2002; Johnson et al., 1989; Kaufman & T'Sjoen, 2002; Neaves et al., 1984).

Sperm parameters

Semen evaluations as total sperm count, daily sperm production, as well as sperm viability, motility, and morphology are all critical parameters that can indicate male reproductive capabilities. All of these parameters were shown to be negatively impacted by the age of the male (Gunes et al., 2016; Rosa-Villagran et al., 2021; Sharma et al., 2015). Indeed, Johnson et al. (2015) conducted an extensive meta-analysis, integrating data from 90 studies, and found that semen volume, sperm mobility and morphology, as well as the percentage of unfragmented sperm, were significantly reduced in aged males compared to young males.

Sperm DNA integrity

Sperm DNA integrity is highly affected by age. Sperm from aged men are found to harbor more chromosomal abnormalities in the form of aneuploidy as well as point mutations (Lowe et al., 2001; McInnes et al., 1998; Rahbari et al., 2016; Wang, Fan, et al., 2012; Yatsenko & Turek, 2018). This is believed to be due to the continuous life-long mitotic and meiotic processes that take place during sperm production and the fact that these cells are exposed to toxins and harmful environmental factors for numerous years (Crow, 2000; Wang, Fan, et al., 2012). Aged males were found to have a higher fraction of sperm with sex chromosome aneuploidy, mainly Klinefelter syndrome (47, XXY) and 47, XYY (Lowe et al., 2001; Martin & Rademaker, 1987). There are also indications for an increased frequency of Down syndrome (trisomy 21) with increased paternal age (Bonduelle, 2002; Fisch et al., 2003; Jyothy et al., 2001). In addition to chromosomal abnormalities, advanced paternal age in humans was shown to negatively impact the level of point mutations in the sperm DNA, leading to single nucleotide changes that can cause pathogenic variants (Marinaro & Schlegel, 2023; Rahbari et al., 2016; Wang, Fan, et al., 2012; Yatsenko & Turek, 2018). Since spermatogonial stem cells undergo ~600–1000 mitotic cell divisions in a period of 20–30 years, it is estimated that on average, a 40-year-old male will accumulate 420 de novo genomic changes over a period of 20 years (Conrad et al., 2011; Kong et al., 2012; Rahbari et al., 2016). This number is likely to increase further with advanced age (Rahbari et al., 2016; Yatsenko & Turek, 2018). Indeed, it was reported that 80% of human structural chromosomal abnormalities in embryos are likely to stem from the sperm (Thomas et al., 2006, 2010). Several studies reported significant higher level of DNA damage in sperm of aged males compared to young males (Johnson et al., 2015; Moskovtsev et al., 2006; Singh et al., 2003). As a consequence, it is suggested that the level of sperm DNA damage is a better indicator of pregnancy success compared to the traditional semen parameters (Giwercman et al., 2010; Muratori et al., 2015).

Fertilization capacity and birth defects

Numerous studies were performed to examine the effect of paternal age on reproductive capacity, both on natural fertilization as well as on ART as insemination, IVF, and intracytoplasmic sperm injection. The effect of maternal age on ART is well-studied (Malizia et al., 2009). However, the effect of the paternal age is less conclusive. Results from these studies are conflicting and while many studies find a significant reduction in fertility of aged males, some do not see evidence to support this (Gunes et al., 2016; Jenkins et al., 2018). In a study conducted in the United Kingdom, it was shown that men older than 45 years old had fivefold increase in their "time to get a pregnancy" compared to males younger than 25 years old (Hassan & Killick, 2003). The situation is further aggravated when the female age is advanced as well. For example, a study that explored both the maternal and paternal age found that in cases where the mother is >35 years and the father is >40, there is a twofold chance to fail to conceive for 1 year period compared to when the males are younger than 40 years old (de la Rochebrochard & Thonneau, 2002). Another big study by De La Rochebrochard et al. examined 3287 couples and found that when paternal age was greater than 40 years old, there was an increased delay in pregnancy onset and conception (De La Rochebrochard et al., 2003; Rochebrochard & Thonneau, 2003). On the other hand, several studies examined the paternal age effect on fertilization and found no significant change (Frattarelli et al., 2008; Olsen, 1990). Paternal age effect was also assessed with regard to success rates of various assisted reproductive techniques and results are again conflicting. While several studies found a significant decrease in ART success rates with advanced paternal age (Belloc et al., 2008; Klonoff-Cohen & Natarajan, 2004; Luna et al., 2009; Mathieu et al., 1995), others did not see an effect (Begueria et al., 2014; Bellver et al., 2008; Whitcomb et al., 2011).

Paternal age was also found to affect early embryonic development. Frattarelli et al. (2008) reported a significant increase in pregnancy loss and a decrease in blastocyst formation rates as well as live birth rates in men older than 50 years of age. Similarly, Simon et al. (2014) showed that increased sperm DNA damage, found in older males, significantly reduced embryo implantation rates. Another effect of advanced paternal age is the risk of abortion. It was shown by several studies that even after correction for maternal age, there is a significantly increased risk of spontaneous abortion with advanced paternal age (Belloc et al., 2008; Kleinhaus et al., 2006; de la Rochebrochard & Thonneau, 2002).

Offspring health

While aged males are mostly capable of having biological children if they try long enough (Gunes et al., 2016; Sharma et al., 2015; Yatsenko & Turek, 2018), one urging question is how advanced paternal age affects the health of the offspring? Several recent studies found a strong correlation between aged males and a higher prevalence of neuropsychiatric disorders, but also other congenital diseases, as well as cancer in the offspring (Gunes et al., 2016; Sharma et al., 2015; Yatsenko & Turek, 2018). D'Onofrio et al. (2014) performed a big population study on 2,615,081 Swedish individuals and found that offspring born to fathers aged 45 years and older had 3.45-fold higher risk to develop autism, 13-fold higher risk to develop ADHD, and 24-fold increase in likelihood to develop bipolar disorder when compared to offspring of fathers aged 20–24 years old. Additional studies found similar findings with a significantly higher risk to develop many neurodevelopmental diseases such as schizophrenia, autism, bipolar disorders, psychosis, suicidal behavior, substance abuse problems along with academic problems (Dalman, 2009; Idring et al., 2014; Miller et al., 2011; Naserbakht et al., 2011). The mechanisms behind these findings are still obscure but they may be due to elevated mutation rates in aged males.

2.2.2 | Epigenetic changes that occur during sperm production

Sperm chromatin

While most somatic cell types in the body contain nucleosomes composed of histones wrapping the DNA, sperm cells possess a unique and highly specified pattern of chromatin structure leading to a 10-fold greater chromatin compaction, which is crucial for the functionality of the sperm (Garrido et al., 2023; Moritz & Hammoud, 2022; Wykes & Krawetz, 2003).

Spermatogenesis is composed of mitosis followed by meiosis and spermiogenesis in which major chromatin rearrangements take place. This process, which is poorly understood, involves the replacement of canonical histones first by testis-specific histone variants, followed by transition proteins (TNPs), and finally by protamines (Moritz & Hammoud, 2022; Wykes & Krawetz, 2003). Protamines are small, arginine-rich, and sperm-specific proteins that wrap the paternal DNA, hence allowing excessive compaction of the DNA in the sperm head (Steven Ward & Coffey, 1991). There are two forms of protamines in most mammals: protamine 1 (P1) and protamine 2 (P2) and the ratio of P1:P2 is highly variable among species but was proven critical for proper fertility (Aoki et al., 2006; de Mateo et al., 2009). Indeed, changes in the P1:P2 ratio in mice and human are associated with increased DNA fragmentation, improper sperm morphology and motility and hence reduced fertilization rates (Arevalo et al., 2022; Grassetti et al., 2012; Merges et al., 2022; Moritz et al., 2021). Interestingly, Paoli et al. (2019) analyzed semen samples from 2626 healthy men aged 20–81 and compared two groups of aged men (50–81 years) versus young men (20–40 years). They analyzed several semen parameters including sperm DNA fragmentation and protamine expression. Aged men showed significantly lower expression levels of protamine 1 and 2 compared to the young men group (Paoli et al., 2019). Interestingly, recent studies indicate that protamines can undergo extensive posttranscriptional modifications (PTMs) including methylation, acetylation, and phosphorylation (Brunner et al., 2014; Moritz et al., 2021; Soler-Ventura et al., 2020). As a result of this unique epigenetic landscape, the sperm chromatin in its final form is compacted into small volume and transcriptionally inactive (Casas & Vavouri, 2014; Grunewald et al., 2005; Moritz & Hammoud, 2022).

Remarkably, not all sperm DNA is bound by protamines and in humans, 5%–15% of the genome remains bound to histones, indicating that in these regions, histones can still affect gene regulation (Gatewood et al., 1987; Hammoud et al., 2009). Furthermore, it seems that the locations of histone retention are not randomly distributed (Arpanahi et al., 2009; Hammoud et al., 2009). Hammoud et al. (2009) showed that histones are mostly retained in developmental gene promoters, imprinted loci, and in genes encoding microRNAs. These regions possess "bivalent" histone modification signatures with both transcription-activating and transcription-silencing histone modifications.

Similar to somatic cells, sperm histones are also decorated by PTMs. It was shown that H3K4me3 marks are enriched in promoters of highly expressed genes during spermatogenesis while H3K27me3 marks mostly developmental regulators such as HOX genes (Hammoud et al., 2009).

Sperm DNA methylation

As with the chromatin landscape, sperm DNA methylation patterns are quite unique. Unlike the intermediate methylation levels found in oocytes (Smallwood et al., 2011), the level of sperm genome methylation is ~70% on average (Lismer & Kimmins, 2023; Molaro et al., 2011; Shea et al., 2015). This methylation is highly critical for the progression of the spermatogenesis process (Barau et al., 2016; Bourc'his & Bestor, 2004; Dura et al., 2022) Yet, specific areas present with hypomethylation, mostly CpG islands of developmental regulatory genes as the HOX genes (Hammoud et al., 2009). Interestingly, aberrant methylation patterns at imprinted loci were found in infertile patients (Pollard & Jenkins, 2020; Santi et al., 2017). In line with this evidence, Aston et al. (2015) compared sperm DNA methylation patterns of 127 men undergoing IVF and divided them into good embryo quality and poor embryo quality following IVF, while filtering out the female effect. They demonstrated that the DNA methylation patterns significantly differ between the two groups with 82% sensitivity and 99% predictive value, indicating that assessing sperm methylation patterns can serve as a biomarker and predictor for male fertility.

2.2.3 | Effects of aging on sperm epigenetics

Cytoplasmic inheritance by the oocyte, including epigenetic regulating molecules, is well established as the oocyte is known to contain

many biomolecules deposited for the offspring (Levy, 2004; de Paula et al., 2013). The sperm, on the other hand, was long considered necessary only for the transfer of haploid DNA. Yet, environmental, and aging effects on the epigenetics of the sperm DNA seem to play a key role in embryonic development and the well-being of the child (Siddeek et al., 2018). Indeed, many studies suggest that alterations in the epigenetic profiles of the sperm may contribute to infertility, poor embryo qualities, and cause offspring pathologies (Aston et al., 2015; Grover & Jenkins, 2020; Jenkins et al., 2016; Jenkins & Carrell, 2012).

Sperm DNA methylation in aging

Changes in sperm DNA methylation are associated with male infertility (Bernhardt et al., 2023; Pollard & Jenkins, 2020; Santi et al., 2017), yet it remains less clear if methylation patterns are altered upon aging. Jenkins et al. (2013) assessed the relative changes in the sperm global DNA methylation levels by examining levels of 5-mC of human sperm at various ages. They show that the global levels of 5-mC significantly increase with age. This study was informative as to the global methylation levels in sperm during aging but could not properly assess changes in the sperm methylation patterns that occur upon aging of the same individual. Hence, the same group later assessed paired samples of sperm from the same individual, collected 9–19 years apart. They analyzed methylation patterns using different approaches as pyrosequencing of LINE, high-resolution CpG array, and targeted bisulfite sequencing. 139 genomic loci were identified that are consistently hypomethylated with age while only eight loci were hypermethylated with age. Altogether, these loci of altered methylation are associated with 117 genes (Jenkins et al., 2014). Remarkably, some of these genes have been previously associated with bipolar disorders and schizophrenia. However, it remains unclear whether the elevated levels of neurological diseases seen in aged males are due to alterations in sperm methylation patterns, and more specifically to the ~140 identified genomic loci.

While causality is hard to assign when working with human samples, this can be better examined in model organisms. Milekic et al. (2015) performed genome-wide DNA methylation analysis on young (90 days old) versus old (360–420 days old) mice and identified a marked decrease in methylation in older mice at regions associated with transcriptional regulation. They further showed that the offspring of older fathers exhibited reduced exploratory behaviors and had dysregulation of genes implicated in human schizophrenia and autism. This study provides a possibility for causality between age-associated sperm DNA methylation changes to neurological disorders. Denomme et al. (2020) also investigated the effect of aged male mice on embryonic placental methylation at imprinted loci. They found that aged mice (330–450 days old) had significant hypermethylation at the *Kcnq1ot1* imprinted locus compared to young mice (120–180 days old).

Interestingly, an evolutionary comparison between human, mouse, and bovine samples with regard to the effect of aging on sperm methylation revealed that most age-related differentially methylated regions are species-specific and not conserved among other species (Prell et al., 2022).

Can these changes in DNA methylation serve as biomarkers or predictors for sperm age and possibly sperm quality? This question has been partly addressed by Jenkins et al. using machine learning approaches. They performed DNA methylation array analysis on 329 sperm samples and used these to train a linear regression age prediction model. This model was trained based on ~50 genomic regions previously shown to be affected by age. Using this model, they demonstrate the ability to predict male age based on methylation patterns with 94% accuracy (Jenkins, Aston, Cairns, et al., 2018). Whether this can serve as a biomarker for predicting fertility capabilities and offspring abnormalities remains to be studied (Grover & Jenkins, 2020; Jenkins, Aston, & Carrell, 2018; Yatsenko & Turek, 2018). Also, further studies are needed to address whether the altered methylation is the cause for reduced fertility and diseases in offspring, or merely associated with aging. In that respect, a recent study assessed the potential of sperm DNA methylation as a predictor of bull fertility. They compared fertile with subfertile bulls and found 490 fertility-related differentially methylated regions, most of which were hypomethylated in subfertile bulls. Based on these sperm DNA methylation patterns, they developed a bull fertility prediction model which presented 72% accuracy rates (Costes et al., 2022).

Sperm chromatin modification in aging

Tatehana et al. (2020) have recently examined histone modification patterns in the germline of young (90 days old) and aged (360 days old) mice using immunostaining. They found decreased intensity of H3K9me3 in aged mice while the H3K27me2/3 marker exhibited increased intensity. The intensity of H3K27Ac was either decreased or increased, depending on the cycle of the seminiferous epithelium stage of the aged testis. Therefore, it seems that aging induces various alterations in the amount of histone modifications (Tatehana et al., 2020).

Interestingly, Katz-Jaffe et al. (2013) analyzed the reproductive capabilities of young versus aged mice and demonstrated a marked decrease in fertilization rates, size of fetuses, and placental weight when the father was older than 360 days old. They also found a decrease in the expression levels of *Ace-1* (Ace-variant 1), *Prm 1* (protamine 1), *Prm 2* (Protamine 2), and *Smcp* (sperm mitochondrial-associated cysteine-rich protein), all key proteins bound to the sperm DNA. It is possible that the decrease in the expression of these sperm-bound proteins is the reason for the decreased fertility capabilities of the aged males. Similarly, Xie et al. (2018) also compared offspring from young (120 days old) and aged male mice (>630 days old). They found that offspring from old fathers had 6.6% reduction in median lifespan, compared to offspring from young fathers. They examined the offspring for the presence of multiple traits of aging, that is, age-related diseases of the heart, arteries, lung, liver, trachea, kidney, skeletal muscle, testis, and brain. These included myocardial fibrosis, glomerulosclerosis, muscle atrophy, testicular atrophy, and others. They found that offspring from aged fathers presented with increased aging traits compared to offspring from young fathers, suggesting that advanced paternal age can

aggravate specific aging-associated changes in tissues. The authors wanted to examine the assumption that incomplete epigenetic erasure during embryonic development may mediate the transfer of age-associated epigenetic alterations. For that aim, they employed reduced representation bisulfite sequencing, genome wide, on sperm of young and old males. This analysis identified 484 promoters with changes in methylation patterns, some of which were hypomethylated (~62%) while others were hypermethylated (~38%) in sperm of old males. Pathway analysis of the altered promoters highlighted several pathways relevant for aging as the mTOR signaling, PTEN signaling, IGF1 signaling, P53 signaling as well as immuno regulatory pathways. Analysis of small noncoding RNA was also performed using RNA-seq and indeed, 428 small RNA were differentially expressed between the sperm of young and old males, some of which were microRNA and others were piwi interacting RNAs. Next, they used chromatin immunoprecipitation sequencing (ChIP-seq) to explore age-related sperm histone occupancy alterations, focusing mostly on H3K4me3 and H3K27me3 in young and aged sperm. A specific locus on chromosome 5 was found to contain 90% of the differential histone posttranslational modifications (Xie et al., 2018).

Finally, they find hyperactivation of the mTOR pathway in aged males and demonstrate that mTOR inhibition can restore some of the age-associated phenotypes seen in offspring of aged males (Xie et al., 2018). Altogether, this work suggests that aged fathers possess many epigenomic changes in the sperm that can be transmitted to the offspring, resulting in a shorter lifespan and an increase in age-associated phenotypes.

2.2.4 | Perspective on sperm aging

During spermatogenesis, the sperm undergoes extensive chromatin remodeling that includes histone replacement by protamines, leading to highly condensed and inaccessible DNA. As such, analyzing patterns of sperm DNA and chromatin poses many experimental challenges. Standard protocols for techniques such as Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq) or ChIP-seq, which were originally developed for somatic cells, do not work well on the dense DNA of the sperm, and require adaptation. The same adaptation is also required in terms of the computational analysis of the data and the biases it contains (Casas & Vavouri, 2014; Hammoud et al., 2009).

It will be interesting to explore the changes in the transcriptome and chromatin landscape that occur during spermatogenesis of young and aged males and how these differ from each other and transmitted to the next generation. Assessing the expression levels and ratio of protamines, as well as other sperm chromatin-bound proteins will be of high interest. A better understanding is also needed as to whether these parameters can serve as biomarkers and predictors of sperm quality.

Once techniques for analyzing sperm chromatin are improved, it will be fascinating to explore the relation between the genomic sites that remain decorated with histones versus those that are packed with protamines. It will be interesting to understand what is unique in these genomic loci that escape the transition, and whether the pattern of histone versus protamines is permanent or changes with age.

Importantly, the option for gamete preservation at young ages via gamete cryopreservation is becoming more and more common with regards to oocytes and many young women consider preserving oocytes for future use. Understanding the major effects of aging on sperm quality could perhaps pave the way for sperm fertility preservation at younger ages.

Lastly, with more data being collected on epigenetic marks of sperm from aged men and DNA methylation patterns, it may be appealing to employ this information as a diagnostic tool to assess sperm quality and allow patients to predict the chances for future complications with pregnancy and health issues of the child.

3 | CONCLUDING REMARKS

Whether for male or for female reproduction, the study of reproductive aging is recently gaining speed, funding, and interest. The current status of the field suggests that many aspects of gamete aging are still open for investigation. The clinical applications of these investigations have far-reaching consequences for fertility and sociological human behavior.

In particular, the field of epigenetic aging of gametes is still mostly an uncharted territory with a promising potential. We have discussed the current knowledge in gamete epigenetic aging and have mapped the unexplored directions in this field.

There is much hope that scientific advances in the understanding of reproductive aging will open the door for parenthood for millions of patients and enable human reproductive longevity.

AUTHOR CONTRIBUTIONS

Michael Klutstein: Conceptualization; funding acquisition; writing—original draft; writing—review and editing. **Nitzan Gonen**: Conceptualization; funding acquisition; writing—original draft; writing—review and editing. Michael Klutstein and Nitzan Gonen wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

M. K. is a cofounder of ForEve Ltd. The remaining author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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